REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 1-17 are pending in the application. Claims 4-17 have been withdrawn from consideration. Claim 1 has been amended to better clarify the invention. Support for the amendment to claim 1 can be found throughout the specification, but particularly on page 2, lines 19-22; on page 5, lines 9-17; in Table 6 on page 19 and in Table 7 on page 22. Accordingly, claims 1-3 are currently under examination. No new matter has been added by way of this amendment.

Claim Rejection under 35 U.S.C. §103

The rejection of claims 1-3 under 35 U.S.C. §103(a) as allegedly being unpatentable over Johnson *et al.* (Journal of Virology, Apr. 1998, Vol. 72, No. 4, pages 2871-2880) in view of Firestone *et al.* (Virology, 1996. Vol. 225, pages 419-422. Article No. 0618, Short Communication) is maintained.

The invention, as currently claimed, is directed to a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F when compared to parent strain A2. The method comprises: providing a eukaryotic cell culture, infecting the cell culture with a live, attenuated RSV strain **at 30°C**; and determining the glycoprotein F concentration in the harvest of the culture, **wherein at least a five-fold increase in glycoprotein F concentration produced when the attenuated RSV strain is grown in the cell culture at 30° C** is an indication that the attenuated strain produces high yields of RSV F glycoprotein when compared with the parent A2 strain **grown at 37°C**. The RSV mutant strain is cpts-248/404. The eukaryotic cell cultures are VERO, MRC-5, FRhL, CEF or PER.C6 cell cultures.

The Examiner's Position

The Examiner alleges that Johnson *et al.* (hereinafter Johnson) teaches the G glycoprotein has been implicated as an RSV antigen that promotes activation of the Th2 CD4+ T-lymphocyte and induces eosinophilic infiltrates in the lung following RSV challenge. The Examiner further alleges that Johnson teaches that the large glycoprotein G serves as the attachment protein of RSV and is one of the major glycoproteins expressed in the membrane of the virus, and is expressed on the surface

of the infected cell and secreted into the extracellular environment. The Examiner also alleges that Johnson teaches use of recombinant vaccinia virus expressing RSV G (vacG) to prime mice, which generated a Th2 CD4+ T lymphocyte response, while vaccination with fusion (F) protein-expressing virus (vacF) induced a Th1 CD4+ T cell response. Furthermore, the Examiner alleges that Johnson also teaches a method of purifying and measuring the G-specific antibody and the secreted RSV G protein from RSV A2 strain, and also teaches that mice vaccinated with vvWTG were found to have more severe illness and weight loss following challenge than mice immunized with vacF. The Examiner also alleges that Johnson teaches a study of viral challenge following vaccination wherein the results indicate that G is less immunogenic than F. The Examiner notes that Johnson does not teach an attenuated RSV, mutant strain cpts-248/404 or using VERO cells to grow the virus.

The Examiner alleges that Firestone *et al.* (hereinafter Firestone) teaches a live attenuated RSV strain, cpts-248/404 mutant, which differs from its wild-type RSV strain A2 by increased G when passaged in VERO cell culture. The Examiner alleges that Firestone compares F content in the live attenuated RSV strain compared to the parent A2 strain. Applicants respectfully note that upon examination of Table 1 on page 421 of Firestone, Applicants could find no such data. The Examiner further alleges that Firestone teaches attenuating RSV and the comparison of wild-type RSV A2 grown in HEp-2 cells, cold-passages cp-RSV, and temperature-sensitive cpts-248. The Examiner also alleges that Firestone teaches how the cpts-248/404 mutant differs from its wild-type RSV A2/HEK7 parent, and that the predominant nucleotide in cpts-248/404 is G and that this can be used for identification of the cpts-248/404 mutant. The Examiner also alleges that Firestone teaches a live attenuated RSV strain, *cpts*-248/404 mutant, which differs from its wild type RSV strain by increased G and F gene content.

The Examiner alleges that it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to identify a high glycoprotein producing RSV. The Examiner alleges that a person of ordinary skill in the art would have been motivated because Johnson teaches the importance of the glycoprotein F and how to measure the glycoprotein, and Firestone teaches a comparison of attenuated RSVs to the wild-type RSV, and as such, one reasonably would have expected success because of the teachings of Johnson and Firestone.

Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness because the references cited by the examiner, when viewed

as a whole, neither teach nor suggest all the claim limitations. In particular, the references do not teach or suggest a method as currently claimed for identifying an attenuated respiratory syncytial virus (RSV) strain that produces a five-fold increase of RSV surface glycoprotein F at 30° C when compared to the yield of glycoprotein F produced by the parent strain A2 grown at 37° C. Moreover, Applicants assert that the references do not teach or suggest that the strain so identified by the methods described in the present invention is *cpts*-248/404, which may be grown in eukaryotic cells selected from VERO, MRC-5, FRhL, CEF or PER.C6 cell culture.

Applicants respectfully traverse the stated grounds for rejection and submit that the combination of Johnson and Firestone, when viewed as a whole, neither teaches nor suggests the subject matter of instant claims 1-3.

Applicants' Position

Johnson

Applicants respectfully traverse the Examiner's rejection and assert that Johnson teaches the use of vaccinia virus vectors that express either wild type G glycoprotein, or soluble/secreted G glycoprotein, or membrane bound G glycoprotein for determining the effect of G priming on immunopathogenesis.

The Examiner has acknowledged that Johnson **does not teach** an attenuated RSV, in particular, *cpts*-248/404, or using VERO cells to grow the virus.

Johnson does not teach or suggest an attenuated respiratory syncytial virus (RSV) strain that produces **a five fold increase in the amount of glycoprotein F.**

Nor does Johnson teach or suggest **any methods comprising growing a strain of RSV at 30°C.**

In addition, Johnson does not teach or suggest **any methods using the *cpts*-248/404 RSV strain.**

Furthermore, Johnson does not teach or suggest **the above methods wherein the strain of RSV is grown in VERO cells, MRC-5 cells, FRhL cells, CEF cells or PER.C6 cells.**

Firestone

Firestone teaches the nucleic acid sequence of the RSV mutant strain *cpts*-248/404. The sequence analysis conducted by Firestone was done in an attempt to determine which nucleotides played a role in temperature sensitivity and/or attenuation

of the virus. **Firestone does not teach or suggest measuring the levels of the F glycoprotein produced by the mutant *cpts*-248/404 strain at 30°C during the course of their work, nor any difference in the levels of the F glycoprotein with the parent A2 strain**. The Firestone reference merely teaches the sequence differences between the various proteins of the parent A2 strain and the mutant strains of the virus to determine whether any of the differences observed could be related to, or associated with, temperature sensitivity or to the attenuation of the virus.

Applicants respectfully point out to the Examiner that Applicants could not find any teaching in the Firestone reference regarding an increase in levels of glycoprotein F by this mutant strain on page 421, Table 1, as noted by the Examiner on page 4, lines 1-3 of the current Office Action. Moreover, Firestone shows in Table 2 on page 421 that the *cpts*-248/404 mutant strain demonstrates reduced titers *in vitro* when grown at 36°C to 39°C. There is no data provided by Firestone that teaches or suggests the enhanced production of the F glycoprotein by the mutant strain when grown at 30°C, as compared to the parent A2 strain.

Firestone **does not teach or suggest a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces a five fold increase in the amount of glycoprotein F at 30°C, when compared to the parent RSV A2 strain grown at 37°C, particularly with the *cpts*-248/404 RSV strain.**

Furthermore, Firestone does not teach or suggest the above method **wherein the strain of RSV is grown in VERO cells, MRC-5 cells, FRhL cells, CEF cells or PER.C6 cells.**

The Analysis under 35 USC 103(a)

To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references, **when combined,** must teach or suggest all the claim limitations. Second, there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the teachings within the references. Third, there must be a reasonable expectation of success in achieving the claimed invention. See MPEP § 2143.

Accordingly, a finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that

the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The arguments advanced by the Examiner fail to meet all of these criteria for the current invention, as presently claimed. More particularly, any rejection based on Johnson and Firestone, in combination, fails for at least the following reasons.

1. There is no teaching or suggestion in the references when combined, for a method of identifying an attenuated respiratory syncytial virus (RSV) strain that produces high yields of RSV surface glycoprotein F, as currently claimed, *e.g.* when grown at 30°C and when compared to the amount of glycoprotein F produced by the parent A2 strain grown at 37°C, using the methods of the present invention, whereby at least a five-fold increase in glycoprotein F concentration is an indication that the attenuated strain, when grown at 30°C, produces high yields of RSV F glycoprotein.

2. There is no teaching or suggestion in the references when combined, for a method of identifying an RSV strain that produces high yields of RSV surface glycoprotein F, as currently claimed, wherein the strain so identified is the RSV mutant strain *cpts*-248/404.

3. There is no teaching or suggestion in the references when combined, for a method of identifying an RSV strain that produces high yields of RSV surface glycoprotein F, as currently claimed, wherein the strain is grown in VERO cells, MRC-5 cells, FRhL cells, CEF cells or PER.C6 cells.

4. There is no motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings found in the cited references to achieve Applicants' claimed invention. Furthermore, the outcome observed through use of the methods of the invention were not known, and **could not be predicted** based on the cited references, given the fact that **neither of the references cited teach or suggest the use of the methods of the invention to identify strains of RSV that demonstrate a five-fold**

increase in production of glycoprotein F of the RSV mutant described herein, when the mutant is grown at 30°C, compared to the amount of glycoprotein F produced by the parent RSV A2 strain, when grown at 37°C. It was only at the time of the present invention that a mutant strain *cpts*-248/404, when grown at 30°C showed an unexpected five fold increase in production of the F glycoprotein.

In sum, the references cited by the Examiner when combined do not teach or suggest the subject matter provided by amended claim 1. In particular, they do not teach any increase in the F glycoprotein by the RSV strains tested, and more particularly, they do not teach a five fold increase in the F glycoprotein by strain *cpts-248/404* at 30° C in any of the cell cultures as currently claimed. Furthermore, neither of the references cited by the Examiner, or the knowledge generally available to one of ordinary skill in the art, would have provided any motivation to combine the teachings of Johnson in view of Firestone in order to achieve the presently claimed invention. More specifically, the references cited by the Examiner would not have suggested to one of skill in the art that a *cpts*-248/404 mutant, which replicates poorly in cells at 37°C, could produce a five fold increase in the F glycoprotein at 30°C, thus making it a highly desirable candidate for vaccine production. In fact, one might predict completely opposite results to those observed with this *cpts*-248/404 attenuated strain, that is, a decrease in production of the F glycoprotein, not an increase, given the fact that this strain is restricted in replication compared to the wild type or parent strain.

Applicants therefore submit that claim 1 is not obvious over Johnson in view of Firestone. Each of claims 2-3 depend from the subject matter of claim 1. Thus, the patentability of each of claims 2-3 under 35 U.S.C. § 103(a) necessarily follows from the non-obviousness of claim 1. Applicants respectfully request that the rejection of claims 1-3 be withdrawn.

Conclusion

It is submitted that the claims are in condition for allowance, and an early and favorable action on the merits is requested. No new matter has been introduced by way of this amendment. In the event that there are any questions concerning this

amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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